Transactions on Materials, Biotechnology and Life Sciences
ISSN: 2960-1932, eISSN: 2960-2319 | Volume 7
MISBP 2024

Nipah Virus: An Overview of What Have Known and Learnt

Yejin Ruan
Admiral Farragut Academy Tianjin, Tianjin, China
ruanpeng@xyzq.com.cn

Abstract. Nipah virus (NiV) is a zoonotic Biological Safety Level 4 (BSL-4) pathogen with a high fatality rate and high risk of transmission, which came into public view during the end of the last century. NiV in human usually results in a series of severe symptoms, from critical respiratory illnesses and acute encephalitis. Pteropus bat species distributed broadly across Asia, Africa and Oceania are the natural hosts of the NiV. Most viral outbreaks are reserved to countries of South and South-East Asia, especially Bangladesh. Molecular examination methods such as RT-PCR and ELISA are effective for the diagnosis of the disease, though some steps should be simplified and revised in order for the assays to become more viable in underdeveloped countries. Currently no cure has been developed for this infectious disease. Diagnosed patients should be given adequate supportive care for better recovery and improved prevention procedures should be acquired in order to prevent further spread of the virus.

Keywords: Nipah virus, clinical symptoms, epidemiology, diagnostic methods, treatment.

1. Introduction

Emerging viral outbreaks have been an essential cause of economic loss and mortality across the globe since centuries ago. After the stringent lockdown due to SARS-CoV-2 since early 2020, more and more infectious diseases have since entered the public view. On 22nd July, 2024, Kerala, health authorities in India announced an alert after the death of a 14-year-old boy due to infection of NiV.

NiV is a biosafety level 4 zoonotic pathogen closely related to the Hendra virus, belonging to the family Paramyxoviridae, subfamily Orthoparamyxovirinae, and to the genus Henipavirus [1]. A virologist group from Universiti Malaya (UM) isolated this virus from a sample from Sungai Nipah (Nipah River Village) in March, 1999. It was then named after the village where it was discovered, Nipah [2]. Later on, the antigenic and serological molecular characteristics of NiV revealed that NiV is cross-reactive against the antibodies of the Hendra virus (HeV) [3].

In 2015, NiV was included in the Blueprint list of eight priority pathogens for research and development. Three years later, the 2018 annual review of the WHO R&D Blueprint suggested that NiV infection was one of the priority diseases due to its high epidemic/pandemic potential. Moreover, NiV has also been marked by the Coalition for Epidemic Preparedness Innovations (CEPI) as one of the vaccine-development urgencies [4].

This passage is an overview of the current information scientists have on the virus and the possible ways of preventing infections of the virus.

2. Symptoms in Human

Currently there are at least two strains of NiV identified: NiV-M (Malaysia) and NiV-B (Bangladesh). Despite them being almost 92% identical when sequenced, their pathogenicity, transmissibility and lethality differs significantly. For instance, in terms of virulence, NiV-M appears to be more infectious than NiV-B, whereas NiV-B has the greater mortality rate of 75% and is more usually correlated with interhuman transmission [5]. NiV-B is most commonly linked to respiratory symptoms such as atypical pneumonia and acute respirational distress. Cephalitis is most frequently found in NiV-M infections [3].

Common NiV infection has an incubation period from 4 to 21 days, most cases have an incubation period less than 15 days. However prolonged incubation periods as long as 60 days have been reported [6]. The disease is always found with a series of symptoms which are non-specific at first, including sore throat, headache, dizziness, vomiting, fever and myalgia. In up to 88% of the patients, fever was found to be universal symptoms. As the infection progresses, severe encephalitis and pulmonary disease can be developed. The encephalitis is primarily characterised by cephalalgia, fever and other neurological symptoms. Brain stem abnormalities, irregular reflexes were also reported in outbreaks. During an infection, after neurological symptoms, the respiratory symptoms are the second most common [3]. Patients who have recovered from the illness constantly suffer from long-term neurological sequelae.

As resurrections of the virus, encephalitis could develop in a few months' time to even years after recovering from a symptomatic initial infection. In recorded cases, encephalitis can develop after up to 11 years after the primary infection [4].

3. Epidemiology

The epidemiology of the NiV is yet to be entirely comprehended and Biosafety level-4 (BSL-4) laboratory facilities are needed for examination. The natural reservoir of the virus are the 60 species of the Pteropodidae family, order Chiroptera [2]. But domestic animals such as dogs, cats, pigs, horses, goats and sheep can also serve as amplifying hosts, making the transmission to humans easier [3, 5]. The transmission of the virus is usually achieved by getting in contact with bodily fluids from infected organisms or consuming food that has been contaminated by the fluids from patients [7]. In multiple NiV spillover events, the occurrence of such incident is primarily due to consumption of uncooked fermented phoenix dactylifera L sap which was polluted by the bodily fluids of infected fruit bats by humans [8].

Overpopulation, over-exploitation of tourism and the lack of hygiene awareness along with environmental factors promoted disease transmission. Severe deforestation has damaged the fruit bats' habitats and food supplies, causing the bat populations to migrate towards more urban areas as a result, therefore increasing the contact of bats with domesticated animals and humans [9]. Furthermore, in Pteropus bats in different regions of Asia and Africa, NiV and Henipa-like viruses have been found. Universal distribution of these bat species could result in the risk of potential global pandemics of NiV.

Sporadic outbreaks of the NiV virus have been documented in Bangladesh, India, the Philippines and Singapore after its initial report and identification during an outbreak among swineherds in the village of Sungai Nipah, Malaysia during 1998 and 1999. The culling of over 1 million pigs was deemed necessary for the control of the pandemic in the initial outbreak, creating a huge burden on the county's and citizens' economy [4].

Until today, these outbreaks are mainly reserved in southeast Asia, especially in Bangladesh and India, as shown in Table 1 below.

Table 1. Total reported NiV outbreaks and cases by country from 1998 to 2024 [10]

Reporting year		Nipah virus strian	Primary source of infection	Predominant clinical presentation	Reported cases	Reported deaths
1999	Malaysia	NiV-M	Interaction with infected pigs	Acute encephalitis	265	105
	Singapore	NiV-M	Interaction with infected pigs	Acute encephalitis	11	1
2001	Bangladesh	NiV-B	Undetermined	Acute encephalitis	13	9
	India	NiV-B	Undetermined	Acute encephalitis	66	45
2003	Bangladesh	NiV-B	Undetermined	Acute encephalitis	12	8
2004	Bangladesh	NiV-B	Eating phoenix dactylifera L sap or fruit contaminated by/contacted with bats	Acute encephalitis	67	50
2005	Bangladesh	NiV-B	As stated before	Acute encephalitis	12	11
2007	India	NiV-B	Undetermined	Acute encephalitis	5	5
	Bangladesh	NiV-B	Eating phoenix dactylifera L sap or fruit contaminated by/contacted with bats	Acute encephalitis	18	9
2008	Bangladesh	NiV-B	As stated before	Acute encephalitis	11	7
2009	Bangladesh	NiV-B	As stated before	Acute encephalitis	4	1
2010	Bangladesh	NiV-B	As stated before	Acute encephalitis	18	16
2011	Bangladesh	NiV-B	As stated before	Acute encephalitis	43	37
2012	Bangladesh	NiV-B	As stated before	Acute encephalitis	17	12
2013	Bangladesh	NiV-B	As stated before	Acute encephalitis	31	25
2014	Philippines	NiV-M	Getting in contact with horse or eating contaminated meat	Acute encephalitis	17	9
	Bangladesh	NiV-B	Eating phoenix dactylifera L sap or fruit contaminated by/contacted with bats	Acute encephalitis	37	16
2015	Bangladesh	NiV-B	As stated before	Acute encephalitis	15	11

2017	Bangladesh	NiV-B	As stated before	Acute encephalitis	3	2
2018	Bangladesh	NiV-B	As stated before	Acute encephalitis	4	2
	India	NiV*	Getting in contact with bats or eating fruit contaminated by bats	Acute encephalitis	18	16
2019	India	NiV*	As stated before	Acute encephalitis	1	0
	Bangladesh	NiV-B	Eating phoenix dactylifera L sap or fruit contaminated by/contacted with bats	Acute encephalitis	8	7
2020	Bangladesh	NiV-B	As stated before	Acute encephalitis	7	5
2021	India	NiV*	Getting in contact with bats or eating fruit contaminated by bats	Acute encephalitis	1	1
	Bangladesh	NiV-B	Eating phoenix dactylifera L sap or fruit contaminated by/contacted with bats	Acute encephalitis	2	0
2022	Bangladesh	NiV-B	As stated before	Acute encephalitis	3	2
2023	Bangladesh	NiV-B	As stated before	Acute encephalitis	14	10
	India	NiV*	Getting in contact with bats or eating fruit contaminated by bats	Acute encephalitis	6	2
2024	Bangladesh	NiV-B	Eating phoenix dactylifera L sap or fruit contaminated by/contacted with bats	Acute encephalitis	2	2
Toal					731	426

4. Viral Structures, Molecular Biology and Pathogenesis of the Virus

4.1. Viral Structures

The fusion protein (F), glycoprotein (G), matrix protein (M), nucleocapsid (N), phosphoprotein (P) and RNA polymerase protein (L) of NiV are determined by six coded genes flanked by a 3’ leader and a 5’ trailer region (3’-N-P-M-F-G-L-5’) contained in the NiV genome. The N, P and L proteins interact with the virus genome to form ribonucleoprotein (RNP) complex. The phosphoprotein gene is responsible for encoding accessory proteins C, V and W. These products are derived from mRNA editing and alternative open reading frames (ORFs). They are important factors in regulating viral RNA synthesis and virulence [3, 5]. The M protein is linked to the inner side of viral envelope, of

which contains the G and F glycoproteins for adhersion to viral entry receptors and fusion. The NiV-G and NiV-F proteins on the viral particles are necessary for the binding and fusion to the target cell. Viral budding is also facilitated by these two proteins [11].

Similar to its close relative the HeV, NiV has a much longer genome of 18.2 kilobases (kb) in length and a broader host range compared to other paramyxoviruses and does not exhibit hemagglutinin and neuraminidase activities of other paramyxoviruses. The mRNA editing site contained in the P gene of the two viruses is identical to that of the morbillivirus. The expression of the V protein is allowed by a single G insertion, while the expression of a protein equivalent to the W protein of Sendai virus is allowed by two G insertions [1]. as shown in Figure 1.

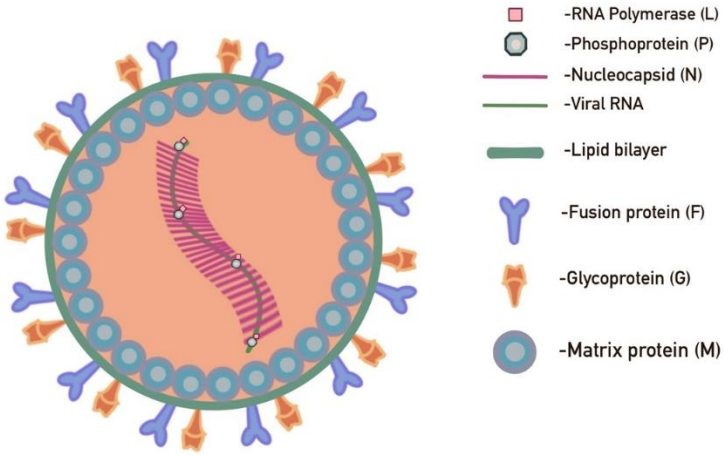

Figure 1. Viral structure (made in Procreate by the author)

4.2. Molecular Biology & Pathogenesis

NiV entry is allowed via absorption mediated by G, H or HN and fusion facilitated by glycoprotein F. The entry receptors NiV uses, Ephrin-B2 and -B3 are highly preserved among numerous mammal species. Once the fusion process is completed, viral genes are expressed in the cytoplasm by glycoprotein L. It is worth noting that NiV is not lymphotropic, unlike some other Paramyxoviridae. Dendritic cells are the only type of blood cells it is able to infect. However, circulating leukocytes are used as a cargo by the NiV for transinfection of the virions. The viral particles attach themselves to passing leukocytes via binding to the heparan sulfate on the surface of leukocytes without infecting them [2]. The M protein manipulates the inner layer of the host cell membrane and conscribes RNP complexes along with transmembrane glycoproteins in order for the assembly and budding process to happen. The N protein encapsulates the RNA of the NiV to form a long helical assembly. Once enough N proteins are produced, viral genome begins to replicate and gets inserted into the capsid through co-transcription of newly assembled N proteins. The G protein undergoes conformational changes and detaches from the F protein during the fusion phase upon receptor binding [11]. Following the preliminary expression at the cell surface and consequent internalisation, the NiV F is manufactured as an inactive precursor F0, and is proteolytically cleaved into two fusion-active subunits, F1 and F2 by a host protease endosomal cathepsin L [1, 12]. The merging peptides are then transferred again onto the surface of the viron to get integrated into the budding virions or to facilitate the cell-to-cell spread of the virus, forming another feature of many paramyxovirus infections, multinucleated syncytia [13].

Among the paramyxoviruses, hepanoviruses are the only ones capable of transmitting zoonotically. The viral particles enter the host through the oral-nasal administration and infect target cells. The oro-pharyngeal lymphoid tissue (Waldeyer's ring) and respiratory system are the primary sites of viral infection. Human bronchial epithelial cells and type II pneumocytes from the respiratory tract were shown in researches to be highly permissive to Henipaviruses and could be the initial target for NiV [2]. Because of the swollen epithelium of the airway, cytokines are secreted, therefore causing the development of acute respiratory distress syndrome (ARDS)-like disorders [12]. Interleukin (IL)-6,

IL-8, IL-1α, the monocyte chemoattractant protein 1 (MCP-1), granulocyte colony stimulating factor (G-CSF) and granulocyte-macrophage colony stimulating factor (GM-CSF) are the key mediators. It is rare that these intermediaries are shown in the trachea and bronchi, therefore low presence of inflammation in cases of respiratory disease is plausible.

High neuro-tropism and the capability of infecting muscular cells is also shown as one of the characteristics of the virus. This suggests that the virus is capable of inducing universal infection in different tissues, which can lead to multi-organ failure [4, 12]. The virion enters in the central nervous system (CNS) through choroid plexus. The blood-brain barrier (BBB) can be disturbed due to infections of this sort. Nonliving viral particles contained in infected CNS can cause necrosis in humans [2]. Indication of direct nerval transmission via the olfactory nerve has also been discovered in experimental swine models [1, 12].

Experimental infections of the NiV in hamsters, ferrets, cats and some larger animals such as horses and pigs, also anthropoid primates like African green monkeys (AGMs) have been done for potential therapeutics developments. Due to its similarities in overall illness progression and symptomatology with NiV-infected humans, the AGM model has been used widely in anti-viral preventive and therapeutic approaches [8].

5. Nipah Virus Diagnosis&Treatment

5.1. Investigation of Infection

NiV disease can be determined by immunohistochemistry, histopathology, virus isolation, serological and molecular diagnostic assays [14, 15]. At earlier stages of disease, viral isolation is allowed through reverse transcription polymerase chain reaction (RT-PCR) and real-time PT-PCR from nasal, throat and cerebrospinal fluid samples from the patient. During acute and recovering stages of the illness, laboratory analyses are effective techniques for diagnosing the infection. Human CSF, blood, nasal/throat swabs, urine are used as samples [14]. IgG-IgM antibody detection by Enzyme-linked Immune Sorbent Assay (ELISA), complete blood workup and serum neutralisation are used for further solidification of the diagnosis, as well as for examination during convalescent phase of infection [3]. Autopsy of tissues followed by an immunobiological analysis is the most sufficient identification approach post death [9].

In addition, because NiV is a Risk Group 4 pathogen, only BSL-4 establishments are capable of running confirmatory diagnostic tests, and specimens containing NiV should be taken charge of using special containment and barrier protection measures. However, since the NiV is relatively labile, samples are sufficient enough to be managed through BSL-2 control methods once the viral particles inside have been killed and inactivated [15].

5.2. Treatment

No licensed anti-viral drugs or vaccines are available for humans or animals at the moment, but various vaccine candidates have been deemed effective in animal models and progressed through phase I and II clinical trials. Most of them target the G and F proteins on viral surface. Adeno-associated virus (AAV)-based vaccines are also being considered because AAV is non-pathogenic and has a high range of tissue tropism.

Two antivirals have also indicated good therapeutic efficacies in non-human primates, with the m102.4 being the most promising. It provides protection against both strains of NiV in 3 to 5 days after challenge [13]. In the experimental ferret model, the attack of neutrialising human monoclonal antibody from post-exposure therapy against the G glycoprotein of the NiV was found to be therapeutically effective [11]. An experiment on the usefulness of mAb against pre-exposure and postexposure of NiV is also undergoing in the US and Australia [9].

Prophylactic treatments to the infection with Ribavirin and other anti-viral drugs against the virus's in-vitro has been proved to be applicable, but the functionality of Ribavirin remains uncertain clinically because of multiple inadequate animal and human studies [2].

As of now, supportive care remains being the main clinical treatment for NiV. Supportive care usually focuses on treating symptoms as they appear and letting the patient get enough rest while staying hydrated.

6. Prevention of the Infection

The first crucial point of preventing the infection of NiV is controlling the vectors and transmission from animals to humans. This can be done by preventing consumption of contaminated date palm sap by covering sap collection pots and using lime as a bat repellent. In order to prevent infected domestic animals from transmitting virus to farmers, strict biosecurity and biosafety measures on farms should be implemented [13].

Secondly, although only about 10% of patients spread the virus to people around them, the diverse transmission still puts those in close contact with patients in danger [8]. Because outbreaks happen mostly in developing countries, proper infection control practices should be enforced in healthcare settings, such as the use of gloves, masks, eye protection and other personal protective equipment. Quick diagnosis and control of the patients are also methods of avoiding human-to-human transmission [8].

Thirdly, people should be educated to avoid direct contact with the sick. Healthcare workers, community members and religious leaders should also be instructed on the importance of following infection control protocols. The effort made on improving public preparedness by the government will also be a key strategy for bettering the prevention of NiV infection [15].

7. Current Chanllenge

Despite now, the practice of more advanced examination methods offer high sensitivity, speed and specificity, very few laboratories in counties where serious outbreaks occur can meet the standards necessary for adopting these procedures [6]. Current conventional techniques can be difficult to execute, laborious and require adequate funding. Training is also needed for the procedures to be performed efficaciously. Ideal instruments for molecular diagnosis should be designed with minimal requirement of operation, making the deployment of these implements to all under-developed epidemic-stricken areas simpler [9].

The low prevalence of NiV disease also presents huge methodological and operational challenges for clinical trials of potential vaccine and drugs against the virus. Even in Bangladesh, where NiV has had the most outbreaks and where the epidemiology of NiV is best understood, NiV infections remain dispersed and unpredictable, the average number of confirmed cases being 14 each year. It is almost impossible for traditional phase 3 efficacy trials to take place under the current epidemiological conditions, let alone further development of efficient cures [10].

8. Conclusion

Nipah virus is a noticeable and dangerous disease with the potential of being the cause of a future pandemic. Growing concerns about these deadly pathogens provoked an increasing amount of investment in vaccine and antiviral development. Immune response and establishment of a protective anti-viral immunity were shown to be efficiently interactable and easily disabled by NiV proteins. With more of these efforts, the discovery and licensing of promising vaccine or drug candidates will significantly lessen the impact of NiV emergences. But until better and deeper understanding of the virus is gained, the ability of humans preventing outbreaks and curing the infection will remain at the same level. Gaining a firmer grasp on both molecular level and cellular level of host-pathogen

relationship in different animal species may open new opportunities of developing inventive anti-viral tactics.

References

[1] Bruno, Luigi, et al. "Nipah virus disease: epidemiological, clinical, diagnostic and legislative aspects of this unpredictable emerging zoonosis." Animals 13.1 (2022): 159.

[2] Ochani, Rohan Kumar, et al. "Nipah virus-the rising epidemic: a review." Infez Med 27.2 (2019): 117-27.

[3] Sharma, Vikrant, et al. "Emerging trends of Nipah virus: A review." Reviews in medical virology 29.1 (2019): e2010.

[4] Pelissier, Rodolphe, Mathieu Iampietro, and Branka Horvat. "Recent advances in the understanding of Nipah virus immunopathogenesis and anti-viral approaches." F1000Research 8 (2019).

[5] Garbuglia, Anna Rosa, et al. "Nipah virus: an overview of the current status of diagnostics and their role in preparedness in endemic countries." Viruses 15.10 (2023): 2062.

[6] Ashwlayan, V. D., and S. Nimesh. "Nipah virus: An update." MOJ Drug Des. Dev. Ther 2 (2018): 211-214.

[7] Conroy, Gemma. "Nipah virus outbreak: what scientists know so far." Nature 10 (2023).

[8] Gurley, Emily S., Christina F. Spiropoulou, and Emmie De Wit. "Twenty years of Nipah virus research: where do we go from here?." The Journal of infectious diseases 221.Supplement_4 (2020): S359-S362.

[9] ayed, A., et al. "Nipah virus: a narrative review of viral characteristics and epidemiological determinants." Public Health 173 (2019): 97-104.

[10] Hassan, Md Zakiul, et al. "Nipah virus disease: what can we do to improve patient care?." The Lancet Infectious Diseases (2024).

[11] Hauser, Naomi, et al. "Evolution of Nipah virus infection: past, present, and future considerations." Tropical medicine and infectious disease 6.1 (2021): 24.

[12] Talukdar, Pratik, et al. "Molecular Pathogenesis of Nipah Virus." Applied biochemistry and biotechnology 195.4 (2023): 2451-2462.

[13] Faus-Cotino, Javier, Gabriel Reina, and Javier Pueyo. "Nipah Virus: A Multidimensional Update." Viruses 16.2 (2024): 179.

[14] Brown, Brent, et al. "Immunopathogenesis of Nipah virus infection and associated immune responses." Immuno 3.2 (2023): 160-181

[15] Shariff, M. "Nipah virus infection: A review." Epidemiology & Infection 147 (2019): e95.